Remarks

Reconsideration and withdrawal of the rejections set forth in the Office Action dated July 19, 2006 are respectfully requested. Claims 29-33 are pending for examination.

I. Double-Patenting Rejection

Claims 29-34 were rejected under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 23-25, 28, and 31 of U.S. Patent No. 6,372,206 ("the '206 patent").

Claims 29-34 were rejected under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 1, 3, and 11 of U.S. Patent No. 5,906,816 ("the '816 patent").

These rejections are respectfully traversed for the following reason.

The Examiner has maintained the rejection on the grounds that the present claims are an obvious species to the methods of treating set forth in the '206 patent and in the '816 patent, and that further distinction is necessary to distinguish between the instant claimed methods and the method of the cited patents.

Applicants provide, as further distinction to distinguish between the instant claimed methods and the method of the cited patents the Examiner requested, two journal articles[1] that establish that lessening the severity of MS is different from preventing a relapse.

In the paper by Young et al. (*Neurology*, 67:804 (2006), attached) the authors investigated whether relapses contributed to the development of subsequent sustained increase of impairment and disability in patients with multiple sclerosis. The authors tested whether time to an increase of the Expanded Disability Status Scale (EDSS) score was related to the occurrence of prior relapses. Young *et al.* concludes that:

> "Our data show that there is no consistent effect of on-study relapses on the subsequent development of sustained EDSS score increase during a typical

[1] Young *et al., Neurology*, 67:804 (2006); Confavreux *et al., New England J. Medicine*, 343:20:1430 (2000), copies attached.

> clinical study observation period..." (page 806, Col. 1, first sentence in Discussion section).
>
> "So we conclude that the impact of relapses on subsequent short-term sustained increase of the EDSS score in patients participating in clinical trials is either non-existent or only minor." (Page 807, Col. 1, first full paragraph).

Thus, based on the conclusion of Young et al. that disease severity, as measured by increased EDSS score, is not related to relapses in MS patients, there is a distinction between "lessening the severity of MS", as set forth in the '206 patent and in the '816 patent, and "preventing a relapse", as currently claimed.

A second journal article by Confavreux *et al.* (*New England J. Medicine*, 343:20:1430 (2000), attached) studied the influence of acute relapses on the rate of progression of irreversible disability in patients with multiple sclerosis. The authors conclude that "Among patients with multiple sclerosis, relapses do not significantly influence the progression of irreversible disability" (p. 1403, Conclusions section). Confavreux *et al.* specifically note an absence of a relation between relapses and irreversible disability, and state:

> "The absence of a relation between relapses and irreversible disability suggests that there is a dissociation at the biological level between recurrent acute focal inflammation and progressive degeneration of the central nervous system." (Page 1437, Col. 1, final paragraph).

Thus, as evidenced by these articles, Applicants maintain that preventing a relapse in a relapsing-remitting MS patient, as presently claimed, is distinguishable from "treating" the disease (i.e., reducing the symptoms of the disease and/or lessening the severity of the disease). For this reason, the present claims are not an obvious variation of the methods claimed in the '206 and the '816 patents.

Applicants hereby respectfully request withdrawal of the rejection of claims 29-33.

II. Conclusion

In view of the foregoing, a Notice of Allowance is respectfully requested. If the examiner has any questions or believes a telephone conference would expedite prosecution of this application, the Examiner is encouraged to call the undersigned at (650) 838-4402

Respectfully submitted,
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Relapses and subsequent worsening of disability in relapsing-remitting multiple sclerosis

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Abstact—*Objective:* To investigate whether relapses contribute to the development of subsequent sustained increase of impairment and disability in patients with multiple sclerosis (MS). *Methods:* In a random sampled subset of 256 relapsing-remitting MS (RRMS) patients from the placebo arms of 20 randomized, controlled clinical trials contained in the Sylvia Lawry Centre for MS Research (SLCMSR) open database (mean follow-up time 2.66 years), the authors tested whether time to an increase of the Expanded Disability Status Scale (EDSS) score (confirmed after 6 months) was related to the occurrence of prior relapses. In the primary analysis, EDSS progressions starting within the period used to calculate the on-study relapse rate (sacrifice period) were not counted. The result obtained was then validated in an independent validation part of the SLCMSR database (n = 320). *Results:* Although in the first subset of 256 RRMS patients, occurrence of relapses in the first 4 months on study appeared to be the best predictor for a shorter time to subsequent sustained increase in the EDSS score (hazard ratio [HR] 2.26 [95% CI: 1.36 to 3.75]), this finding was not confirmed in the validation dataset (HR 1.35, one-sided Wald test, lower limit of the 95% CI: 0.90). *Conclusion:* Although relapses may result into permanent damage and Expanded Disability Status Scale (EDSS) progression, there is no consistent effect of on-study relapses on the subsequent development of sustained EDSS score increase during a typical clinical study observation period.

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For most patients, multiple sclerosis (MS) starts as a relapsing-remitting (RR) disease that in about 80% eventually transforms to the secondary progressive phase characterized by relentless increase in disability with or without superimposed relapses.[1,2]

Recent studies have suggested that, after a certain degree of disability is reached, relapses have no impact on long-term disability progression.[3,4] Nevertheless, there still is an active debate whether relapses during the RR phase are associated with a more rapid subsequent increase in sustained neurologic dysfunction.

Obtaining an answer to this issue would both facilitate recruitment of active and thus informative patients to clinical trials with disability progression as endpoint and give important insight into the mechanisms underlying disability development in MS. Moreover, it might help to better understand the impact of currently approved disease-modifying agents that do significantly reduce relapse rates,[5-9] whereas evidence supporting an effect on the reduction of, especially not directly relapse associated, sustained increase in impairment and disability as usually depicted by change in the Expanded Disability Status Scale (EDSS) score[10] remains less convincing.[7-9,11]

Natural history studies[1,12-15] have not demonstrated an unequivocal effect of relapses on long-term disability, and relatively little work has been conducted with clinical trial data.[16] Data derived from the placebo groups of clinical trials might be particularly well suited because typically frequent assessments of relapse activity and disability have been performed under well-standardized conditions.[17] We present both the results in the open part and the validation in the closed part of the Sylvia Lawry Centre for MS Research (SLCMSR) database.

Methods. *Definition of relapse.* Because different randomized, controlled trials (RCTs) in our database have used (slightly) different inclusion criteria (i.e., at least one or two relapses required over a 1- or 2-year period prior to study entry), it is difficult to obtain an unbiased estimate of association between the relapse rate prior to study entry and sustained increase of the EDSS score during the study. In addition, the prior relapse data are often collected retrospectively and are therefore less reliable than the prospectively collected on-study relapse data. For these reasons, we decided to use only on-study data for this analysis. In all studies from which data were used, on-study relapse data had

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been collected under strict and essentially similar methods as specified in the respective study protocols.

Sacrifice period. We were unsure of the optimum period of time at the start of the study that should be used to calculate the initial on-study relapse rate. Because most studies used either a 3- or 6-month regular visit interval, we decided to consider four possibilities: the first 80 (minimum 80 days), 120, 160, and 200 days. We named this period the sacrifice period. Considering a period longer than 200 days did not seem sensible because it appeared likely that this would sacrifice too much data to the estimation of the relapse rate and not leave enough to gain a reasonable estimate of the subsequent rate of sustained increase in the EDSS score.

Patient selection and definition of disability endpoint. At the time that this analysis was conducted the SLCMSR database contained data on the placebo arms of 20 RCTs. We restricted our analysis to RRMS patients. We required that eligible patients must have at least 1 year of follow-up data to be included. A sustained increase in the EDSS score[6] was defined as a ≥ 1 point increse in the EDSS score (0.5 if baseline >5.5), confirmed by another visit at least 135 days later.[18] (Because most patients had visit intervals of about 3 months, this is nearly equivalent to 180 days' confirmation, but this definition seemed to be more appropriate to cover also irregular visit schedules of some patients.)

The baseline value was the value at entry into the study. In the main analysis, we excluded patients who had undergone a relapse related to a confirmed increase in the EDSS score, but starting before the end of the sacrifice period. A second analysis was performed with the data for patients who had undergone a relapse related to a confirmed increase in the EDSS score that had started within the sacrifice period included. In calculating the relapse rate for the sacrifice period, we only accepted relapses that started within this time span. Where the exact start of a relapse was not clearly defined but only the window of time in which it occurred, we have multiplied the number of relapses that were recorded in this time window (this was the case for 11, 11, 14, and 18 relapses for time windows of 80, 120, 160, and 200 days) by the proportion of the time window that overlapped with the sacrifice period.

The primary analysis consisted of dividing patients into two groups defined by whether they experienced more than a certain number of relapses during the sacrifice period. Here we considered two possibilities. Partitioning based on those who had zero relapses vs those who had more than zero relapses in the sacrifice period and a split based on those who had up to one relapse vs those who had more than one relapse. A two-sided log rank test was conducted to determine whether the time to sustained increase in EDSS score was different for these two groups. The estimate of the hazard ratio (HR) was also presented along with corresponding significance levels and 95% CIs.[19]

Validation procedure. In providing data for statistical research, the SLCMSR has adopted the following policy in order to prevent the possibly substantial bias of exploring data and then performing, using the same dataset, formal statistical tests for hypotheses that were suggested by such explorations: The dataset is randomly split into an open part and a closed part: The open part is used to generate hypotheses and the second (closed or validation) part is for validating specific, well-defined hypotheses. The authors had direct access only to the open dataset for the initial series of studies (hypothesis testing). Having performed all of these 8 tests (four different sacrifice periods × two different cutpoint splits), we then selected the one that gave the lowest p value. As this p value was significant, the authors submitted their program code to the SLCMSR's Data Trustee, who then performed a validation on the closed dataset (hypothesis validation) using the programs and software provided by the authors. The data trustee only returned the resulting p value, total number of subjects, and estimated HR to the authors. Because this validation was performed on a specific one-sided hypothesis generated from the open part of the SLCMSR dataset, a one-sided Wald test was used in the validation. The Wald test was preferred over the log rank test because the validation should also provide a CI for the effect. A CI, in case of significance, allows demonstrating that the observed effect of relapses is not only significant but even exceeds a clinically relevant threshold. All computations were performed using the SAS software (version 8.2) for Windows and R software (version 2.01) for Linux.

Table 1 Comparison of patients in the open and closed datasets

	Open dataset	Closed dataset
No. (M/F)	256 (65/191)	320 (96/224)
Mean follow-up, d (SD)	972 (305)	972 (309)
Mean no. of visits (SD)	14.3 (4.8)	13.9 (4.8)
Mean entry EDSS score (SD)	2.8 (1.4)	2.8 (1.4)
Mean no. of relapses in prior 2 y	3.1 (1.4)	3.0 (1.4)
Mean age at baseline, y	35.3 (7.8)	35.3 (7.8)
Mean disease duration, mo	86.1 (76.4)	87.1 (73.6)
After applying sacrifice period of 120 d		
No. with no relapse (confirmed progressions)	158 (29)	213 (48)
No. with >0 relapse (confirmed progressions)	83 (32)	90 (26)

EDSS = Expanded Disability Status Scale.

Results. *Open dataset analysis.* The first part of the analysis is based on a randomly selected subset of 256 RRMS patients from the open part of the SLCMSR database. It consists of data from 20 clinical trials for which on-study information concerning relapses was available (see Acknowledgment section). In order to preserve confidentiality of the data donor, it is a policy of the SLC that all data are made anonymous at the time of donation to the center so that it is not possible to identify the individual sources of the data within the analysis. Information was also available on the following covariates: age at study entry (years), duration of MS at study entry (years), EDSS score at study entry (range 0 to 6 due to study inclusion criteria), gender, and number of relapses in the 2 years prior to study entry (collected retrospectively at baseline). Table 1 presents the demographics of the patients in the open and validation datasets: patients are typical of those enrolled in clinical studies in RRMS. The mean follow-up time in both datasets was 972 days (SD = 305,309; median = 820, IQR = 327, minimum = 711, maximum = 1,778 in the open and median = 818, IQR = 341, minimum = 700, maximum = 1,848 in the validation dataset). In the open and validation datasets also, mean baseline EDSS score, mean number of available visits, number of relapses in prior 2 years, age at baseline, and disease duration were virtually identical (table 1).

Tables 2 and 3 show the p values obtained for the eight tests that were conducted and the associated number of patients in each arm of the comparison. In table 2, patients who had an increase in the EDSS score during the sacrifice period that was confirmed at least 135 days later were excluded from the respective test (as noted above), so the numbers in each arm of the comparison do not add up to 256. Table 3 shows the same calculations but with those patients who started progression within the sacrifice period accepted, thus calculated in a similar way as in Lublin et al.[16]

Tables 2 and 3 show that a significant effect occurs as soon as the split is not too unbalanced. For the validation, we chose a 120-day sacrifice period combined with a zero vs at least one relapse split, which was considered a compromise between having a balanced split, having reliable information about the on-study relapse, and not losing too many patients due to the sacrifice period.

The direction of the result of the log rank test was that

Table 2 Description of the analyses conducted on the open part of the SLCMSR database: Progressions starting within the "sacrifice period" not included

	Sacrifice period							
	80 days		120 days		160 days		200 days	
Split	Split (events)	*p* Value (two-sided)	Split (events)	*p* Value (two-sided)	Split (events)	*p* Value (two-sided)	Split (events)	*p* Value (two-sided)
0 vs >0	183 (45) vs 69 (27)	0.016	158 (29) vs 83 (32)	0.0012	145 (28) vs 96 (33)	0.027	127 (22) vs 107 (32)	0.062
≤1 vs >1	244 (69) vs 8 (3)	0.53	219 (53) vs 22 (8)	0.17	209 (49) vs 32 (12)	0.033	196 (39) vs 38 (15)	0.0048

Two splits were performed: No relapse vs occurrence of relapse in the sacrifice period and fewer than one relapse vs one or more. In each cell of the table, the upper line indicates the number for the low relapse group and in parentheses, the number of sustained progressions in this group. The lower line gives the number for the higher relapse group and in parentheses the number of sustained progressions in this group. *p* Values refer to a two-sided log rank test.

SLCMSR = Sylvia Lawry Centre for MS Research.

patients with at least one relapse subsequently had a shorter time to reach a sustained increase of the EDSS score (estimated HR 2.26, 95% CI: 1.36 to 3.75). Consequently, the figure shows a clear separation of the hazard curves. As expected, the analysis in table 3), which allows for a direct impact of the discriminating relapse on progression, reaches in all comparisons higher significance levels

Validation in the closed dataset. When the results obtained according to table 2) in the open dataset for a 4-month sacrifice period and a split of no relapse vs at least one relapse were tested in the independent (closed) validation dataset (n = 320; one-sided Wald test), it was not validated (p = 0.109). We estimated the power of the validation test, e.g., the probability of verifying a significant effect of relapses on subsequently developing impairment/disability without any further assumptions about the closed dataset, except for the number of eligible patients. If the true HR was set as found in the open dataset (2.26), the power was 97% (one-sided Wald test); if the HR was set as 1.36 (lower 95% confidence limit in the open dataset), the power still was 37%.

Discussion. Our data show that there is no consistent effect of on-study relapses on the subsequent development of sustained EDSS score increase during a typical clinical study observation period; moreover, the failure to confirm the initial result underlines the importance of validating in an independent sample results obtained through a hypothesis-generating approach.

We must take into account that the clinical trials used for this study were of relatively short duration (mainly 2 to 3 years), and thus our results consider the relatively short-term accrual of disability or impairment and may not be directly applicable to considerations about the relationship of relapses and development of disability over longer periods of 5, 10, or more years.[1,3,12] Importantly, however, the observations of modest reduction in on-study relapse rates shown by randomized controlled trials of similar short duration (1 to 3 years) have resulted in licensure and wide use of four immune-modulating agents. Our findings suggest that the premise that treatment-related reductions in relapse rate will delay or lessen disability progression in RRMS patients merits further careful study.

Our data also question the rationale for using prior relapse rate as an inclusion criterion in clinical trials as a means to enrich the study population with patients who are more likely to experience a sustained increase in their EDSS level. Nevertheless, it should be kept in mind that patients recruited for these studies were already preselected as having had relapses in the previous 1 to 2 years.

In order to interpret the apparent contradiction between the two results obtained in the open dataset and the validation dataset correctly, one has to consider both the effect of multiple testing on the open dataset and the power of the validation.

It was not possible to adjust for the effects of multiple testing in the open dataset due to the likely correlation between the eight hypotheses. Moreover,

Table 3 Description of the analyses conducted on the open part of the SLCMSR database: Progressions starting during the sacrifice period are counted together with subsequent progression (definition as in Lublin et al.[16])

	Sacrifice period							
	80 days		120 days		160 days		200 days	
Split	Split (events)	*p* Value (two sided)	Split (events)	*p* Value (two sided)	Split (events)	*p* Value (two sided)	Split (events)	*p* Value (two sided)
0 vs >0	184 (46) vs 72 (30)	0.005	163 (34) vs 93 (42)	0.00005	149 (32) vs 107 (44)	0.002	134 (29) vs 122 (47)	0.007
≤1 vs >1	247 (72) vs 9 (4)	0.23	232 (66) vs 24 (10)	0.14	222 (62) vs 34 (14)	0.06	211 (54) vs 45 (22)	0.0007

SLCMSR = Sylvia Lawry Centre for MS Research.

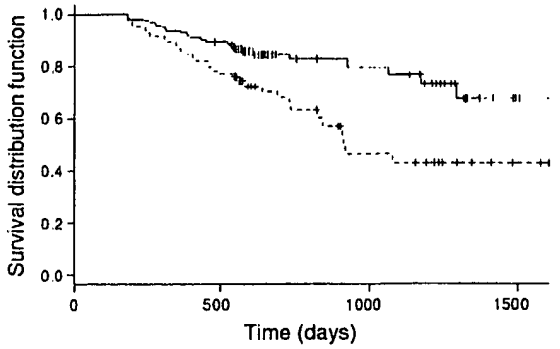

Figure. Kaplan-Meier plot of time to sustained increase in the Expanded Disability Status Scale score (open dataset). Main analysis method excluding patients with progressions starting during the sacrifice period. Solid line, no relapse in the sacrifice period (first 120 days on study; n = 158, 29 confirmed progressions); dotted line, more than 0 relapses in the sacrifice period (n = 83, 32 confirmed progressions).

the true number of hypotheses, which were implicitly tested just by looking at the data, cannot be quantified. So the low p value obtained on the open dataset gives only perfunctory significance, which, without further confirmation, should not be considered valid.

Assuming the same total proportion of events as in the open dataset, but taking the case numbers of the closed part as a basis (n = 213 for the no relapse arm and n = 90 for the relapse arm), the power to detect a significant difference between these arms in the validation dataset would have been 97% for the one-sided Wald test at α = 5%, assuming the estimated HR of 2.26 would be the true HR. Assuming a smaller HR of 1.5 (which still could be considered clinically relevant because it is of the order of magnitude of treatment effects), the power would have been 54%. So we conclude that the impact of relapses on subsequent short-term sustained increase of the EDSS score in patients participating in clinical trials is either nonexistent or only minor.

In the London Ontario dataset,[1,14] an impact of a high initial relapse rate (five or more within the first 2 years) on later disability was described. This is not in contradiction to our findings as the patients included in our study were all in later phases of the disease. This higher correlation of relapse activity and EDSS progression in early as opposed to later phases of the disease seems to be a genuine difference seen in other datasets[3,4] and also in work describing the correlation of MRI signs of (inflammatory) disease activity and disability.[20,21]

The data and conclusions from our main analysis seem to be different from those obtained in another study that addressed a similar question in a group of 224 patients from the placebo groups of several clinical trials.[16] In this study, relapses were found to result in measurable and sustained effects on disability. One major difference in the design of the two studies is that these authors[16] did consider the residual deficit resulting from the initial relapse itself, whereas in our main analysis, we focused on disability that developed after the index relapse; therefore, this initial deficit resulting from the index relapse was excluded from analysis. To directly compare the two approaches, we repeated the analysis of table 2, allowing the residual deficit from the initial relapse to be considered (table 3). As expected, this analysis resulted in p values, typically lower by a factor of 10 as compared to those in table 2.

We believe that the two approaches complement each other and take into account that disability can progress in two ways[22]: In the absence of inflammation and relapses, disability may occur as a result of chronic demyelination and axonal stress leading to degeneration, but disability may also occur as a direct consequence of acute inflammatory events (relapses) causing axonal transections and mediating a more direct damage. That latter way of disability progression would be at least partly lost by our main analysis method, especially in a relatively short follow-up period.

This study has addressed the impact of relapses on in-trial EDSS. Given the fundamental importance of the question, additional studies are needed to assess the long-term impact of relapses on disability progression. The results suggest that full understanding of the relationship of relapses to unremitting progression will also require in-depth study of the meaning, and definition of EDSS changes such as those currently used in MS trials.

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RELAPSES AND PROGRESSION OF DISABILITY IN MULTIPLE SCLEROSIS

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ABSTRACT

Background The influence of the patterns of onset of multiple sclerosis and relapses of the disease on the time course of irreversible disability is controversial.

Methods In 1844 patients who had had multiple sclerosis for a mean (±SD) of 11±10 years, we determined the time of the clinical onset of the disease, the initial course (relapsing–remitting or progressive) and the subsequent course (relapsing–remitting, secondary progressive, or primary progressive), the times of relapses, the time to the onset of irreversible disability, and the time course of progressive, irreversible disability. We used three scores on the Kurtzke Disability Status Scale (range, 0 to 10, with higher scores indicating more severe disability) as measures of the severity and progression of disability: a score of 4 (limited walking ability but able to walk more than 500 m without aid or rest), a score of 6 (ability to walk with unilateral support no more than 100 m without rest), and a score of 7 (ability to walk no more than 10 m without rest while leaning against a wall or holding onto furniture for support). We used Kaplan–Meier analyses to determine the influence of relapses on the time to the onset of irreversible disability.

Results The median times from the onset of multiple sclerosis to the assignment of a score of 4, a score of 6, and a score of 7 on the disability scale were longer among the 1562 patients with a relapsing–remitting onset of disease (11.4, 23.1, and 33.1 years, respectively) than among the 282 patients who had progressive disease from the onset (0.0, 7.1, and 13.4 years, respectively; $P<0.001$ for all comparisons). In contrast, the times from the assignment of a score of 4 to a score of 6 were similar in the two groups (5.7 and 5.4 years, $P=0.74$). The time course of progressive, irreversible disease among patients with the primary progressive type of multiple sclerosis was not affected by the presence or absence of superimposed relapses.

Conclusions Among patients with multiple sclerosis, relapses do not significantly influence the progression of irreversible disability. (N Engl J Med 2000; 343:1430-8.)

MULTIPLE sclerosis is the most common chronic disabling disease of the central nervous system in young adults. It affects 1 in 1000 people in Western countries.[1] It is primarily characterized by multicentric inflammation and demyelination, but the role of axonal injury and gliosis increases as the disease evolves.[2] In most patients the disease begins at about 30 years of age with acute episodes of neurologic dysfunction, followed by periods of partial or complete remission with clinical stability between relapses — the relapsing–remitting phase of the disease. Except in patients with the relapsing–remitting type of multiple sclerosis, this phase is usually followed by progressive clinical disability, with or without superimposed relapses and remissions.[3-5] In a minority of patients, the disease is progressive from the beginning, although there may be superimposed relapses and remissions. Therefore, neurologic disability may result from relapses with incomplete remissions, progression of the disease, or both.

Since 1993, two drugs — interferon beta and glatiramer acetate — have been identified as disease-modifying treatments.[6-10] These drugs reduce the frequency of relapses by about one third but are less effective in slowing the progression of disability.[8-10] The objective of this study was to determine the influence of acute relapses on the rate of progression of irreversible disability in patients with multiple sclerosis.

METHODS

Patient Population and Data Collection

Patients were identified through the Lyons multiple sclerosis data base.[3] This computerized surveillance system was established in 1976 and includes all patients with a diagnosis of multiple sclerosis who were examined at least once at the Clinique de Neurol-

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ogie in Lyons, France. This clinic has served as the referral center for multiple sclerosis for the city of Lyons and the Rhône–Alpes region since 1976. Decisions regarding diagnostic tests and treatments for individual patients were made by referring neurologists or neurologists in the clinic, or both, according to accepted guidelines. Relapses were usually treated with glucocorticoids. Since the late 1960s, azathioprine and cyclophosphamide have been used to treat multiple sclerosis. Azathioprine is administered mainly during the relapsing–remitting phase of multiple sclerosis and after the third relapse, and it is usually stopped when the disease becomes progressive. Cyclophosphamide therapy is used only in severe cases or during the progressive phase of the disease. A single, intense course may be given, or long-term treatment may be given, but it usually lasts no longer than 12 months. Since the early 1990s, methotrexate has been used, usually for no more than 12 months, in some patients with the secondary progressive type of multiple sclerosis.

Each case report in the data base includes identifying and demographic data, medical history, key episodes in the course of the disease (relapses, onset of progressive disease, and onset of irreversible, progressive disability), results of laboratory and electrophysiologic tests, neuroimaging data, and treatment. Data are entered retrospectively when the patient is first seen at the clinic and at each follow-up visit, usually on a yearly basis. Since 1990, data have been recorded on the standardized computerized forms designed for the European Database for Multiple Sclerosis.[11] New data are automatically compared with older information, and any inconsistencies are identified. The confidentiality of the data is maintained in accordance with the recommendations of the French Commission Nationale de l'Informatique et des Libertés. All patients gave informed consent to have their data included in the data base.

Definition of Cases

By April 1997, 2021 patients had been included in the data base. Multiple sclerosis was diagnosed according to the classification of Poser et al.[12] This classification scheme relies on three criteria: dissemination of lesions in time (there must be at least two distinct neurologic episodes in the course of the disease); evidence of spatial dissemination of lesions in the central nervous system, provided by clinical findings or magnetic resonance imaging, computed tomography, or testing of evoked potentials; and quantitative or qualitative abnormalities of immunoglobulins in the cerebrospinal fluid. Cases are considered clinically definite when the first two criteria are met, regardless of the results of cerebrospinal fluid tests; laboratory-supported definite cases meet the first and third criteria or the second and third criteria; clinically probable cases meet the first criterion or the second criterion; laboratory-supported probable cases meet the third criterion; and possible cases do not fulfill any of the criteria but are characterized by neurologic abnormalities that are compatible with the diagnosis of multiple sclerosis.

Assessment of Patients

A relapse of multiple sclerosis was defined as the occurrence, the recurrence, or the worsening of symptoms of neurologic dysfunction that lasted more than 24 hours and that stabilized or eventually resolved either partially or completely. Fatigue alone and transient fever-related worsening of symptoms were not considered relapses. Symptoms that occurred within a month after the initial symptoms of relapse were considered to be part of the same episode.

The onset of progressive disease was defined as a continual worsening of symptoms and signs for a period of at least six months, with or without superimposed relapses.[13] Once progression has developed, its course is continuous, although occasional plateaus and temporary minor improvements may occur.[5]

Neurologic disability was assessed at each visit to the clinic with use of the Kurtzke Disability Status Scale,[14] which is based on the results of a neurologic examination and the patient's ability to walk. Scores can range from 0 (no neurologic abnormality) to 10 (death from multiple sclerosis). We focused on scores that could

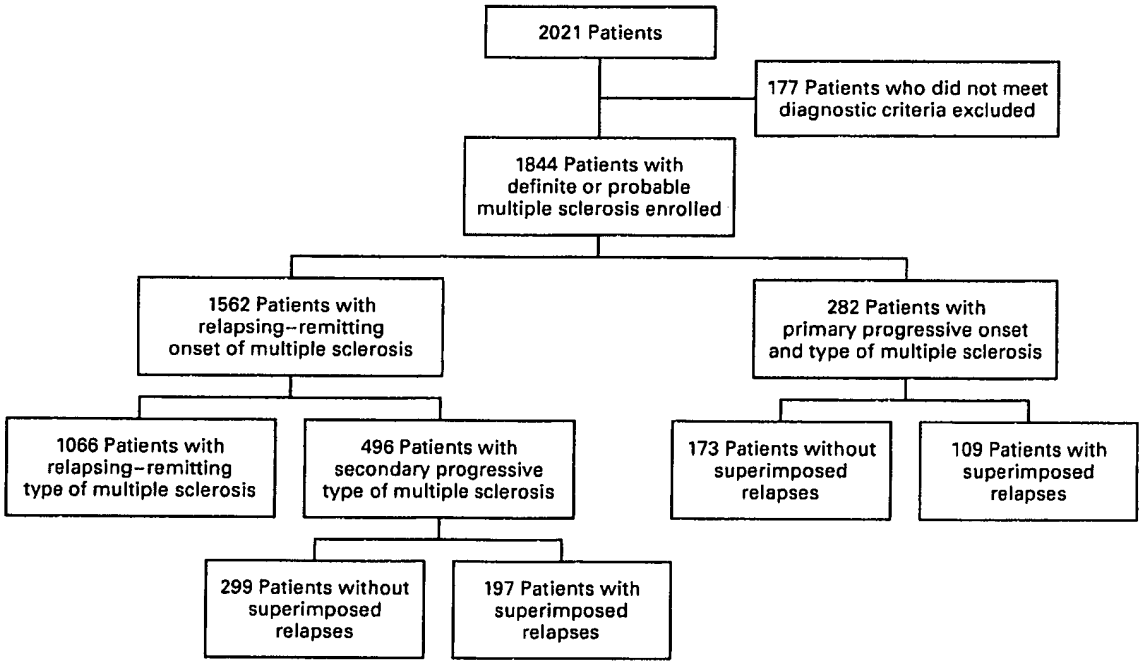


Figure 1. Overall Course and Type of Multiple Sclerosis in the Study Patients.

be easily determined retrospectively: scores of 4 (limited walking ability but able to walk without aid or rest for more than 500 m), 6 (ability to walk with unilateral support no more than 100 m without rest), and 7 (ability to walk no more than 10 m without rest while leaning against a wall or holding onto furniture for support). Disability was defined as irreversible when a patient had had a given score for at least six months, excluding any transient worsening of disability related to relapses.

Statistical Analysis

Survival was estimated according to the Kaplan–Meier method, and the log-rank test was used for univariate analyses. The end point was the time to irreversible disability, as indicated by a score of 4, 6, or 7 on the Kurtzke Disability Status Scale. All computations were performed with the use of SPSS software for Windows (version 9.0).[15]

RESULTS

Characteristics of the Patients

Of the 2021 patients who were potentially eligible for the study, 170 were excluded because they had possible cases according to the classification of Poser et al.[12] and 7 were excluded because their initial symptoms were unknown (Fig. 1). The base-line characteristics of the remaining 1844 patients with a definite or probable diagnosis of multiple sclerosis are given in Table 1.

A total of 903 patients (49 percent) had received one or more drugs for multiple sclerosis. The most widely used treatment was azathioprine (given to 820 patients), followed by cyclophosphamide (given to 78), interferon beta (given to 72), methotrexate (given to 60), and mitoxantrone (given to 18). As compared with the patients who had not received such drugs, the treated patients had a higher frequency of relapses and a more severe initial course of the disease, findings that presumably reflect a selection bias with respect to the use of drug therapy. Treatment status did not affect the results of our analyses. However, it should be noted that the only treatment with proven efficacy is interferon beta, and the first of these interferons, interferon beta-1b, was not available in our area until February 1996. Moreover, the treatment regimens were heterogeneous, and treatments were usually given for fairly short periods relative to the overall duration of the disease in a given patient.

Initial Course of Multiple Sclerosis and Time to Onset of Irreversible Disability

A total of 1562 patients (85 percent) had relapsing–remitting disease initially, whereas 282 patients (15 percent) had progressive disease. In the entire group of 1844 patients, the median time from the onset of multiple sclerosis to the assignment of a score of 4 on the Kurtzke Disability Status Scale was 8.4 years (95 percent confidence interval, 7.8 to 9.6). The median time from onset of multiple sclerosis to the assignment of a score of 6 was 20.1 years (95 percent confidence interval, 18.1 to 22.5), and the median time from the onset of disease to the assignment of a score of 7 was 29.9 years (95 percent confidence interval, 25.1 to 34.5). The median interval from the onset of disease to the assignment of each of these scores was significantly longer ($P<0.001$ for each comparison) in the group of patients with a relapsing–remitting onset of disease than among those who had progressive disease at onset (Table 2 and Fig. 2).

TABLE 1. BASE-LINE CHARACTERISTICS OF THE 1844 PATIENTS WITH MULTIPLE SCLEROSIS.*

CHARACTERISTIC	VALUE
Sex — no. (%)	
Male	657 (36)
Female	1187 (64)
Age at onset of multiple sclerosis — yr	
Mean	31±10
Median	30
Range	5–67
Initial symptoms — no. (%)	
Isolated optic neuritis	335 (18)
Isolated brain-stem dysfunction	159 (9)
Isolated dysfunction of long tracts	964 (52)
Combination of symptoms	386 (21)
Course at onset of multiple sclerosis — no. (%)	
Relapsing–remitting	1562 (85)
Progressive	282 (15)
Time from onset of disease to initial clinic visit — yr	
Mean	6±8
Median	3
Range	0–53
Kaplan–Meier estimate of time from onset of disease to second neurologic episode — yr	
Mean	6
Median	2
Range	0–63
Duration of multiple sclerosis — yr	
Mean	11±10
Median	9
Range	0–63
Type of multiple sclerosis — no. (%)	
Relapsing–remitting	1066 (58)
Secondary progressive	496 (27)
Primary progressive	282 (15)
Diagnosis — no. (%)†	
Clinically definite	1125 (61)
Laboratory-supported definite	251 (14)
Clinically probable	365 (20)
Laboratory-supported probable	103 (6)

*Plus–minus values are means ±SD.

†The diagnoses were classified according to the method of Poser et al.[12]

Initial Course of Multiple Sclerosis and the Time Course of Progressive, Irreversible Disability

Among the 1844 patients, 1026 patients (56 percent) reached the end point of a score of 4 on the Kurtzke Disability Status Scale during follow-up. In this group, the median time from the assignment of a score of 4 to the assignment of a score of 6 was 5.7 years (95 percent confidence interval, 5.0 to 6.3). The median time from the assignment of a score of 4 to the assignment of a score of 7 was 12.1 years

TABLE 2. KAPLAN–MEIER ESTIMATES OF THE MEDIAN TIME FROM THE ONSET OF MULTIPLE SCLEROSIS TO THE ONSET OF IRREVERSIBLE DISABILITY AMONG 1844 PATIENTS WITH MULTIPLE SCLEROSIS, ACCORDING TO THE INITIAL COURSE.*

VARIABLE	RELAPSING–REMITTING ONSET			PROGRESSIVE ONSET			P VALUE†
	NO. OF PATIENTS (N=1562)	MEDIAN TIME (95% CI)	PATIENTS WHO DID NOT REACH THE END POINT‡	NO. OF PATIENTS (N=282)	MEDIAN TIME (95% CI)	PATIENTS WHO DID NOT REACH THE END POINT‡	
		yr	%		yr	%	
Time from onset of multiple sclerosis to assignment of a score of 4	1562	11.4 (10.5–12.3)	52	282	0.0	4	<0.001
Time from onset of multiple sclerosis to assignment of a score of 6	1562	23.1 (20.1–26.1)	73	282	7.1 (6.3–7.9)	40	<0.001
Time from onset of multiple sclerosis to assignment of a score of 7	1562	33.1 (29.2–37.0)	82	282	13.4 (11.0–15.9)	64	<0.001
Time from assignment of a score of 4 to assignment of a score of 6	755	5.7 (4.9–6.4)	44	271	5.4 (4.3–6.6)	38	0.74
Time from assignment of a score of 4 to assignment of a score of 7	755	12.1 (10.0–14.2)	63	271	12.0 (10.1–13.9)	62	0.70
Time from assignment of a score of 6 to assignment of a score of 7	426	3.3 (2.8–3.9)	37	169	4.0 (2.9–5.1)	42	0.48

*The Kurtzke Disability Status Scale was used to determine the extent of disability.[14] On this scale, a score of 4 indicates limited walking ability but able to walk without aid or rest for more than 500 m, a score of 6 indicates the ability to walk with unilateral support for no more than 100 m without rest, and a score of 7 indicates the ability to walk no more than 10 m without rest while leaning against a wall or holding onto furniture for support. Disability was defined as irreversible when a patient had had a score of 4 or more for at least six months, excluding any transient worsening of disability related to relapses. CI denotes confidence interval.

†P values were calculated with use of the log-rank test.

‡Data on patients who had not reached an end point were censored at the time of the last clinic visit.

(95 percent confidence interval, 10.3 to 13.9). Similarly, 595 patients (32 percent) reached the end point of a score of 6. In this group, the median time from the assignment of a score of 6 to the assignment of a score of 7 was 3.4 years (95 percent confidence interval, 3.0 to 3.8). The median times required for each of these changes to occur were similar whether the disease was initially relapsing–remitting or progressive (Table 2 and Fig. 2).

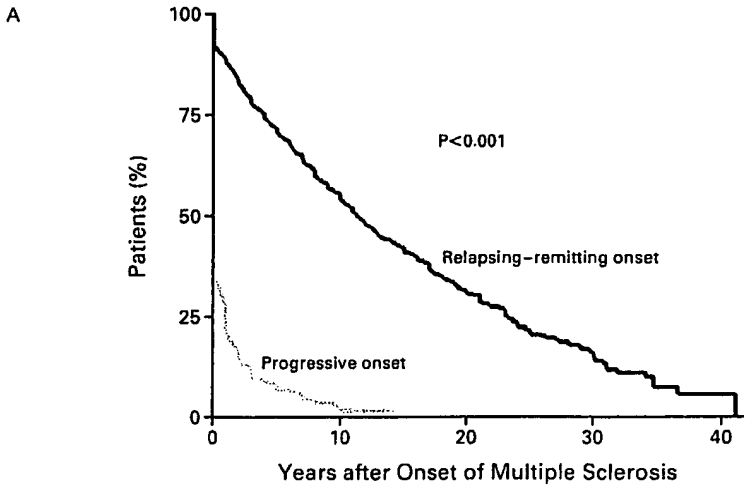
Effect of Superimposed Relapses during the Progressive Phase on the Time Course of Progressive, Irreversible Disability

Among patients with the secondary progressive type of multiple sclerosis, the median time from the assignment of a score of 4 on the Kurtzke Disability Status Scale to the assignment of a score of 6 was not influenced by the presence or the absence of superimposed relapses (Table 3 and Fig. 3). In contrast, the median time from the assignment of a score of 4 to a score of 7 and from a score of 6 to a score of 7 was longer among patients with the secondary progressive type who had superimposed relapses than among patients with this type of multiple sclerosis who did not have superimposed relapses (Table 3). Among patients with the primary progressive type of multiple sclerosis, the median time from the assignment of a score of 4 to a score of 6 or 7 or from a score of 6 to a score of 7 was not influenced by the presence or the absence of superimposed relapses (Table 3 and Fig. 3).

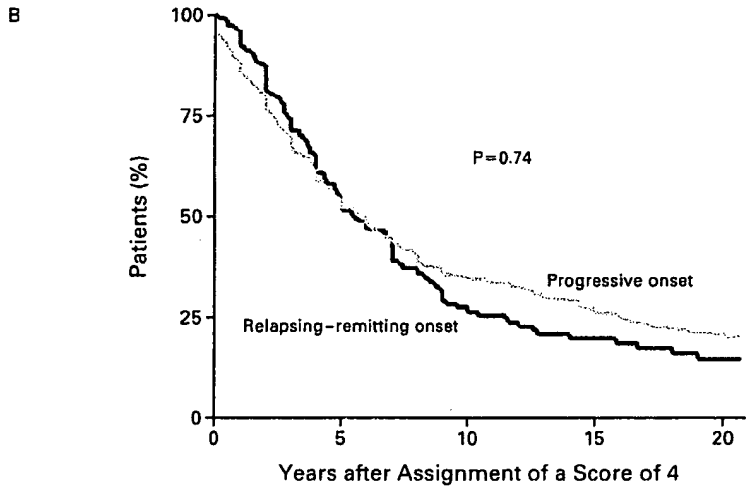
DISCUSSION

In this observational study of the natural history of multiple sclerosis, we found that irreversible disability occurred sooner in patients in whom the disease was progressive from its onset than in those in whom the onset was relapsing–remitting. In contrast, once irreversible disability occurred, the time course of progressive disability was similar in the two groups. In addition, the time course of progressive, irreversible disability among patients with the primary progressive type of multiple sclerosis was not significantly influenced by the presence or absence of superimposed relapses. Among patients with the secondary type of multiple sclerosis (which occurs after a relapsing–remitting phase), the time course of the progressive phase of the disease was longer among patients who had superimposed relapses than among those who did not have superimposed relapses.

The Lyons multiple sclerosis data base is probably among the largest and oldest of such registries. Data



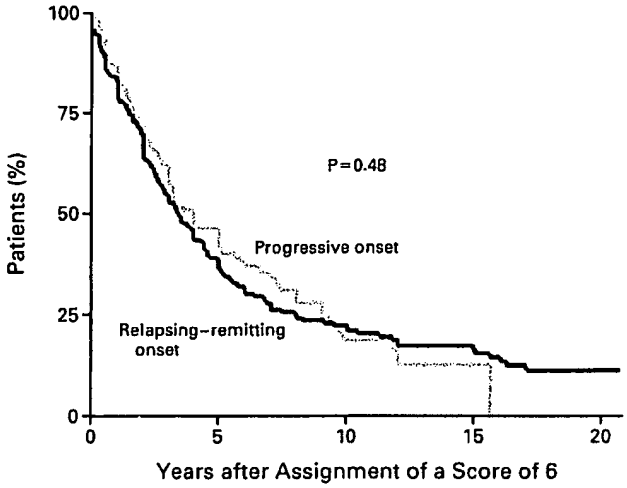
No. at Risk					
Relapsing–remitting onset	1562	479	116	22	1
Progressive onset	282	2	0	0	0



No. at Risk					
Relapsing–remitting onset	755	255	114	54	27
Progressive onset	271	103	36	18	10

Figure 2. Kaplan–Meier Estimates of the Time from the Onset of Multiple Sclerosis to the Assignment of a Score of 4 on the Kurtzke Disability Status Scale (Panel A), the Time from the Assignment of a Score of 4 to a Score of 6 (Panel B), and the Time from the Assignment of a Score of 6 to a Score of 7 (Panel C) among 1844 Patients with Multiple Sclerosis, According to the Initial Course.

C



No at Risk					
Relapsing–remitting onset	426	93	31	15	4
Progressive onset	169	41	9	1	0

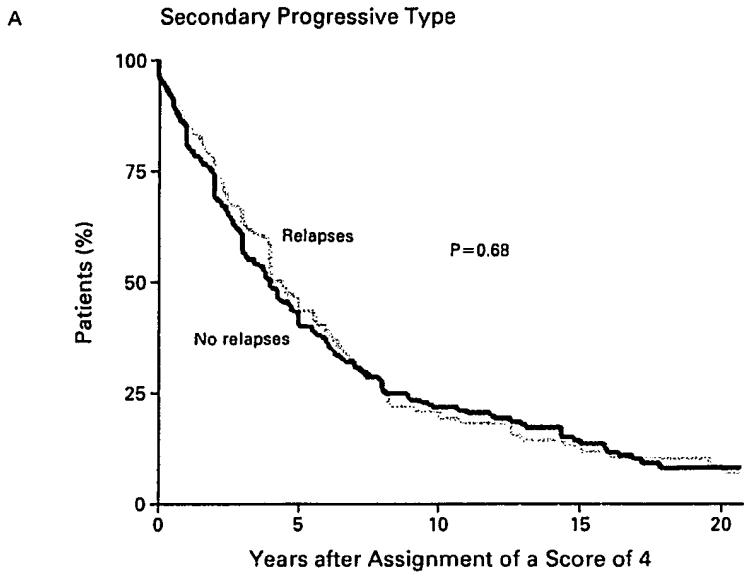
TABLE 3. KAPLAN–MEIER ESTIMATES OF THE MEDIAN TIME COURSE OF PROGRESSIVE, IRREVERSIBLE DISABILITY AMONG PATIENTS WITH THE PRIMARY OR SECONDARY TYPE OF PROGRESSIVE MULTIPLE SCLEROSIS, ACCORDING TO THE PRESENCE OR ABSENCE OF SUPERIMPOSED RELAPSES.*

VARIABLE	PROGRESSIVE COURSE WITHOUT SUPERIMPOSED RELAPSES			PROGRESSIVE COURSE WITH SUPERIMPOSED RELAPSES			P VALUE†
	NO. OF PATIENTS	MEDIAN TIME (95% CI)	PATIENTS WHO DID NOT REACH THE END POINT‡	NO. OF PATIENTS	MEDIAN TIME (95% CI)	PATIENTS WHO DID NOT REACH THE END POINT‡	
		yr	%		yr	%	
Secondary progressive type							
Time from assignment of a score of 4 to assignment of a score of 6	292	4.0 (3.1–4.9)	24	191	4.4 (3.9–5.0)	31	0.68
Time from assignment of a score of 4 to assignment of a score of 7	292	7.8 (6.8–8.7)	42	191	10.0 (7.6–12.4)	55	0.04
Time from assignment of a score of 6 to assignment of a score of 7	223	2.6 (2.1–3.1)	27	133	4.3 (3.0–5.7)	38	0.002
Primary progressive type							
Time from assignment of a score of 4 to assignment of a score of 6	163	5.5 (4.5–6.5)	36	108	5.4 (3.3–7.5)	40	0.71
Time from assignment of a score of 4 to assignment of a score of 7	163	12.4 (10.2–14.7)	63	108	11.3 (7.8–14.7)	61	0.65
Time from assignment of a score of 6 to assignment of a score of 7	104	4.0 (2.8–5.2)	44	65	3.6 (2.2–5.0)	38	0.68

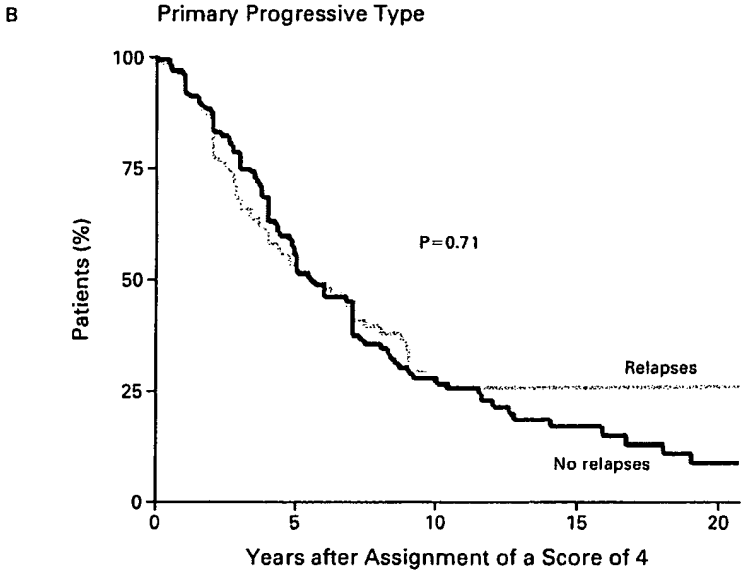
*Among the 496 patients with the secondary progressive type of multiple sclerosis, only 483 reached the end point of a score of 4 during follow-up. Among the 282 patients with the primary progressive type of multiple sclerosis, 271 reached this end point. The Kurtzke Disability Status Scale was used to determine the extent of disability.[14] On this scale, a score of 4 indicates limited walking ability but able to walk without aid or rest for more than 500 m, a score of 6 indicates the ability to walk with unilateral support for no more than 100 m without rest, and a score of 7 indicates the ability to walk no more than 10 m without rest while leaning against a wall or holding onto furniture for support. Disability was defined as irreversible when a patient had had a score of 4 or more for at least six months, excluding any transient worsening of disability related to relapses. CI denotes confidence interval

†P values were calculated with use of the log-rank test.

‡Data on patients who had not reached an end point were censored at the time of the last clinic visit.



No. at Risk					
No relapses	292	92	39	17	7
Relapses	191	56	19	9	4



No at Risk					
No relapses	163	61	22	7	3
Relapses	108	42	14	8	5

Figure 3. Kaplan–Meier Estimates of the Time from the Assignment of a Score of 4 on the Kurtzke Disability Status Scale to the Assignment of a Score of 6 among the 496 Patients with the Secondary Progressive Type of Multiple Sclerosis (Panel A) and the 282 Patients with the Primary Progressive Type of Multiple Sclerosis (Panel B), According to the Presence or Absence of Superimposed Relapses.

Among the 496 patients with the secondary progressive type of multiple sclerosis, only 483 reached the end point of a score of 4 during follow-up. Among the 282 patients with the primary progressive type of multiple sclerosis, 271 reached this end point.

on patients with multiple sclerosis who were referred to and subsequently followed in the clinic are entered in the data base by a group of neurologists who use commonly accepted guidelines and a standardized approach.[11] In terms of their demographic characteristics, clinical course, and prognosis, our cohort of patients is similar to those in other major published studies.[4,16,17]

The first validated disease-modifying drug for multiple sclerosis, interferon-beta 1b,[6] became available in France in February 1996. Approximately half of our patients have received immunosuppressive drugs — azathioprine, in most cases — for some period of time; none of these drugs have a commonly recognized specific effect on the course of multiple sclerosis.[18]

Our results are in accordance with and extend those of other large studies of the natural history of multiple sclerosis. A group of Canadian researchers showed that, as compared with patients with the primary progressive type of multiple sclerosis, patients with the secondary progressive type had a slower onset of disability but a faster progression of the disability.[19] The same group also showed that the survival curves were almost identical for patients with the primary progressive type of multiple sclerosis who had superimposed relapses and patients with the primary progressive type who did not have superimposed relapses with respect to the time from the onset of disease to the assignment of a score of 6, a score of 8, and death.[20] Others have reached similar conclusions with respect to the time from the onset of primary progressive multiple sclerosis to the assignment of a score of 6.[21]

Relapses and progression are the two basic clinical phenomena of multiple sclerosis. Relapses are considered to be the clinical expression of acute inflammatory focal lesions disseminated in the central nervous system, whereas progression is considered to reflect the occurrence of demyelination, axonal loss, and gliosis. We found that once a clinical threshold of irreversible disability has been reached (a score of 4 on the Kurtzke Disability Status Scale), the progression of disability is not affected by relapses, either those that occur before the onset of the progressive phase or those that supervene during this phase. The absence of a relation between relapses and irreversible disability suggests that there is a dissociation at the biologic level between recurrent acute focal inflammation and progressive degeneration of the central nervous system. This apparent paradox is consistent with the persistence of the progression of disability in patients with multiple sclerosis despite infection with the human immunodeficiency virus[22] or despite suppression of the cerebral inflammation after treatment with a potent antileukocyte monoclonal antibody.[23] It also suggests that agents that have a short-term effect on relapses in patients with multiple sclerosis may not necessarily delay the development of disability in the long term.

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